LETTERS TO THE EDITOR

Angina pectoris and oesophageal angina

EDITOR,—I enjoyed the prospective study by Cooke *et al* (*Gut* 1998;**42**:323–329) on the relation between oesophageal abnormalities and chest pain in patients with normal coronary angiograms and with angina pectoris. This study confirms the findings of previous studies[1 2] that the oesophagus is responsible for chest pain in a high percentage of patients with coronary artery disease, and that an episode of gastro-oesophageal reflux nearly always triggers this pain.

However, no explanation for this unexpected finding has been given. The tentative proposition that it is the result of a decreased angina threshold[3] and a reflex coronary ischaemia, both induced by the contact of acid with the oesophageal mucosa, is not acceptable for two reasons: firstly, because this oesophagocardiac reflex may be the basis for linked angina but not for oesophageal angina and, secondly, because the patients should have shown simultaneous electrocardiographic (ECG) abnormalities during the pain induced by the acid perfusion test. Unfortunately, a concurrent ECG was not performed during pH monitoring. This intriguing finding gives rise to two questions: why do these patients have such a high incidence of gastro-oesophageal reflux and why does this so frequently cause them pain?

I believe that the first question can be answered by the fact that patients with angina pectoris are usually prescribed long term medication such as nifedipine or nitroderivatives; these drugs are potent inhibitors of lower oesophageal sphincter tone, which is the main antireflux barrier. It would be interesting to know whether the patients with angina from Cooke and colleagues' study had taken this type of medication for long periods, and whether their lower oesophageal sphincter tone was below normal at the time of the study. In a previous study, we measured manometrically the lower oesophageal sphincter tone in patients with angina after a drug washout, and found a significantly lower value than normal.[5] It seems probable that the chronic consumption of spasmolytic drugs may have reduced this tone, giving patients with coronary artery disease the appearance of pathological gastro-oesophageal reflux. Furthermore, it is possible that the absence of oesophageal spastic disorders, such as nutcracker oesophagus, could be attributed to the long term pharmacological suppression of oesophageal contractile activity.

With regard to the second question, it is very odd that patients with angina and gastro-oesophageal reflux complain mainly of retrosternal pain instead of the more common symptoms of gastro-oesophageal reflux—for example, heartburn, acid regurgitation, etc.[6] Previous studies have shown that there is a decrease in the pain perception threshold of patients with oesophageal angina and normal coronary angiograms,[7] but we do not know whether pain perception in patients with oesophageal angina and coronary artery disease is similarly altered. I would expect a positive result from research on this matter, because it is not unreasonable to suppose that chronic cardiac pain may have sensitised the nociceptive neurones of the dorsal horn of the spinal cord,[8] where the nociceptive fibres coming from the oesophageal mucosa also converge, thus developing a secondary hyperalgesia allodynia.[9] Should spinal hyperalgesia be present, episodes of gastro-oesophageal reflux that are generally not perceived to cause pain, could simulate the pain of angina.

M BORTOLOTTI
Department of Internal Medicine and Gastroenterology, University of Bologna, Via Massarenti 48, 40138 Bologna, Italy

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Intrahepatic HCV levels in chronic HCV infection

EDITOR,—Haydon *et al* (*Gut* 1998;**42**:570–5) have found that hepatitis C virus (HCV) RNA is present in the liver of 87% of unselected patients with circulating anti-HCV antibody (confirmed by recombinant immunoblot assay) and negative serum HCV RNA by polymerase chain reaction (PCR). Furthermore, 70% of these patients had normal serum alanine aminotransferase (ALT) concentrations. Previous experience from both our group and others would suggest that most of these patients would be HCV RNA negative in liver tissue, whether treated or untreated.[1–3] In fact, Fong and colleagues have shown that eight patients with anti-HCV antibody, persistently normal ALT concentrations (mean 14.5 months), and negative serum HCV RNA, had no HCV RNA detectable in liver or peripheral lymphocytes using qualitative reverse transcriptase (RT) PCR.[2] Recently, we used a multi-cycle RT PCR (SuperQuant, National Genetics Institute, Culver City, CA, USA) to quantify HCV RNA in both liver and serum. Ten untreated patients with detectable anti-HCV antibody (including one patient who was coinfected with HIV) were negative in serum using the SuperQuant assay: eight of these patients had raised ALT concentrations, and all had a liver biopsy sample taken. Liver tissue samples were assayed for HCV RNA and nine patients were negative in liver tissue. Three additional patients had negative serum for HCV RNA (Roche Amplicor, Roche Molecular Systems) and had no detectable liver HCV RNA (SuperQuant). However, using the SuperQuant assay, small amounts of HCV RNA (all less than three logs) were found in their serum. We speculate that this more sensitive assay might have amplified extrahepatic viral sequences.[4]

Based on our data, we believe that most patients with negative HCV RNA in serum will be found to be HCV RNA negative in liver, particularly when ALT concentrations are normal. Furthermore, very sensitive assays may detect small quantities of HCV RNA (which may be extrahepatic in origin) in serum but not in liver.[4]

M BONACINI
A G REDEKER
USC School of Medicine Liver Unit, Downey, California, USA

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Reply

EDITOR,—We thank Drs Bonacini and Redeker for their interesting comments and data. Their study, which used a multi-cycle RT PCR assay with a detection sensitivity of 100 copies HCV RNA/ml serum, showed that only one patient out of 10 with detectable anti-HCV antibody was positive in liver tissue, when concurrently negative in serum.

Using a limiting dilution assay (which has already been proved to have significant reproducibility when multiple samples are tested in duplicate, and a significant correlation with three commercial assays[1]) with a detection sensitivity of 80 HCV copies/ml of serum (in a 5 ml sample of serum), we showed that 10 out of 12 patients who were RT PCR negative in serum, were RT PCR positive in liver. Significantly, all 12 patients had ongoing inflammation, diagnosed by diagnostic laparoscopy and from liver biopsy samples.

We would be interested to know the histological findings taken from the liver biopsy samples in Dr Bonacini's study; ongoing hepatic inflammation indicates the continued presence of the virus in very small quantities. We maintain our hypothesis that such patients are viraemic below the detection sensitivity level of the above assays (which is similar, although the assays have not been compared), and that it is impossible to be certain that the infection has been cleared completely even at a detection sensitivity of 100 copies HCV/ml.

However, the prognostic importance of these data is that serum RT PCR negative

patients, with chronic HCV infection, need to be followed up for an indefinite period because there is no indication that they are immune from progressive liver disease in the future.

G H HAYDON
Department of Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK

1 Hawkins A, Davidson F, Simmonds P. Comparison of plasma loads among individuals infected with hepatitis C virus genotypes 1, 2 and 3 by quantiplex HCV RNA assay versions 1 and 2, Roche Monitor assay, and an in-house limiting dilution method. *J Clin Microbiol* 1997;**35**:187–92.

Is exposure to a patient with Crohn's disease an environmental factor for developing the disease?

EDITOR,—A recent study of intestinal permeability in patients with Crohn's disease, their spouses, and first degree relatives, has concluded that baseline permeability is influenced by environmental factors, whereas permeability provoked by acetylsalicylic acid is genetically determined (*Gut* 1999;**44**:96–100). The significance of increased intestinal permeability is still unclear, but animal models show that it may be an early event in the inflammatory process, suggesting that environmental and hereditary factors interact in the pathogenesis of Crohn's disease.

This study also observed that baseline permeability in relatives who were not living with the patient with Crohn's disease at the time of diagnosis, or at the time of the permeability test, was considerably less abnormal than that of relatives who lived with the patient. Similarly, a subcategory of spouses who had lived with their Crohn's disease partners since before diagnosis, had a higher percentage of increased permeability than other spouses.

Previously, increased occurrence of Crohn's disease in a patient's relatives has been assumed to be indicative of genetic predisposition, and has not been linked to frequency of contact. A study of clusters of cases from the same family suggested that, based on a temporal succession of presentations, an infectious microorganism might be involved.[1] Several studies have proposed that spouses of patients with Crohn's disease show a higher frequency of the disease than expected[2–4]; however, these studies were based on estimates of disease prevalence and could be influenced by under-reporting of such cases. Clusters of unrelated patients with Crohn's disease who shared a close relationship or lived in the same community before developing the disease have also been reported.[5 6]

Finally, a study of disease transmission in animal models also indicated that Crohn's disease may have an infectious aetiology. It showed consistently that animals inoculated with isolates from patients with Crohn's disease developed chronic intestinal inflammation, whereas animals inoculated with isolates from patients with ulcerative colitis or other gastrointestinal diseases did not[7]; this inflammation could be prevented by addition of an antibiotic (ampicillin) to the inoculate.[8]

The establishment of a positive correlation between intestinal permeability in spouses and relatives and the length of association and frequency of contact with patients with Crohn's disease could resolve whether development of the disease is due to this environmental factor. Thus, it may be useful to perform an observational study which compares the frequency, length, and nature of contact between all first degree relatives and the patient with Crohn's disease. Soderholm *et al*'s study of intestinal permeability included only 34 of 123 first degree relatives of 39 patients with Crohn's disease, because many relatives had little social contact with the patients. It is only through an exhaustive search for all relatives that frequency of contact between patients with Crohn's disease and relatives who have the same genetic predisposition towards the disease can be linked to the risk of developing the disease. Such a study may also resolve whether earlier onset of the disease in familial cases, compared with time of onset in people who develop Crohn's disease independently, is caused by genetic anticipation or environmental factors.

M ALIC
1754 S Grant #4
San Mateo, CA 94402, USA

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Reply

EDITOR,—We thank Dr Alic for his interesting comments on our study of intestinal permeability in relatives and spouses of patients with Crohn's disease. We agree that Crohn's disease may be part of an infectious process, and our study does not contradict this hypothesis. One of our conclusions was that baseline permeability may be a function of unknown environmental factors that could be directly related to contact with, or factors shared with, the patients with Crohn's disease—for example, an infectious agent or dietary factors.

As Dr Alic suggests, we have further analysed the relation between length of exposure of the spouses and relatives to the patients with Crohn's disease and baseline permeability in these people (table 1). We found that all spouses with an increased baseline permeability (above the 95th percentile of controls) had lived with their Crohn's disease partner for more than 10 years. However, a study of the relatives showed that there was no link between length of time living with the patient and baseline permeability. Neither group showed any correlation between permeability after ingestion of acetylsalicylic acid and time of exposure to patients.

Table 1 Number of spouses with high and low baseline intestinal permeability in relation to duration of cohabitation with patients with Crohn's disease

	Normal L:M	*High L:M*	*Total*
Less than 10 years	9	0	9
More than 10 years	8	5*	13
Total	17	5	22

Permeability is expressed as the lactulose:mannitol ratio (L:M). *Increased number compared with less than 10 years; p=0.054; Fisher's exact test.

We also agree that a search for all the relatives of all of our patients with Crohn's disease would provide more information. A group from Belgium has performed a thorough study of all relatives of a group of such patients[1]; they showed increased baseline permeability in subgroups of both first degree relatives and spouses, and suggested a common environmental factor as the cause. In conclusion, we cannot exclude a transmissible factor as the cause of increased baseline permeability, although it is not known whether this accounts for permeability provoked by acetylsalicylic acid, although our data do not indicate an environmental cause.

Does the increase in baseline, and/or provoked, permeability predispose the spouse or relative towards developing Crohn's disease? This is a different and more difficult issue to tackle. It has yet to be established whether a sustained increase in intestinal permeability can trigger inflammation, but circumstantial evidence is in favour of this as a possible mechanism. Knockout mice which are deficient in N-cadherin (an adhesion molecule important for epithelial structure) develop intestinal inflammation that resembles Crohn's disease.[2] Moreover, we have found that inflammation in recurrent Crohn's ileitis is preceded by increased epithelial permeability to proteins.[3] However, further studies are needed to explain the pathogenic importance of increased epithelial permeability to the development of mucosal inflammation in Crohn's disease.

In the past 10 years, several studies have shown subgroups of relatives with increased baseline permeability,[4–8] and four studies have shown increased mucosal reactivity to non-steroidal anti-inflammatory drugs in first degree relatives.[9–12] A multicentre follow up study of the relatives included in these studies could discover whether relatives with increased baseline and/or stimulated permeability will eventually contract disease.

J D SODERHOLM
G OLAISON
R SJODAHL
Department of Surgery, University Hospital, S-581 85 Linkoping, Sweden

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